an increased incidence of carcinoma of the lung were asbestos workers, moulders and foundrymen, and chromate workers, and pointing out that asbestos and chromate contain varying amounts of iron in their chemical composition. In this context there is further support from the work of Campbell (1940, 1943), who exposed mice of a strain susceptible to lung cancer to an atmosphere laden with ferric oxide. He found that 32.7% of the mice exposed to the dust developed tumours of the lung compared with 9.6% of the controls, while mice exposed to a mixture of silica and ferric oxide showed a tumour incidence halfway between these figures (19.4%).

*Mode of Action of Iron.*—It has been observed that the histiocytes at the site of injection and elsewhere in the body (for example, Kupffer cells) contain, in addition to iron pigment, globules of a lipofuscin pigment of ceroid nature. The development of ceroid throughout the tissues of the body is one of the characteristics of vitamin-E deficiency (Mason, 1944), and in recent experiments Golberg and Smith (1958) have shown that the ceroid developing through iron overload can be largely prevented by supplementing the diet with $\alpha$-tocopherol. It may therefore be inferred that one way in which iron influences intracellular metabolism is by blocking the antioxidant activity of vitamin E and possibly other antioxidants in the cell. The destruction or interference with these natural antioxidants allows oxidation of unsaturated fats to form the yellow pigment which is termed ceroid (Casselman, 1951). It remains to be shown whether this action of iron in the cell has any relation to the development of malignant change.


## Summary

In the adult rat weekly-repeated intramuscular injections of iron–dextran complex induced sarcoma at the site of injection. A bi-weekly series of similar injections, begun in weanling rats and stopped after 12 weeks, also induced sarcoma at the site of injection some seven months later.


I wish to thank Professor J. S. Young for continuous encouragement and advice during this work, and Professor A. Haddow for a helpful discussion and the personal communication of his observations on the mouse. My thanks are also due to Mr. A. Bodie, senior technician, for his co-operation, and to Miss E. M. Gillies, who carried out much of the technical work. Mr. W. Topp kindly supplied the photographs.

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# MELIOIDOSIS


BY

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[WITH SPECIAL PLATE]

Melioidosis is an uncommon yet highly lethal disease caused by *Pfeiferella whitmori*, which closely resembles the organism responsible for glanders in animals. The disease was first reported by Whitmore and Krishnaswami in 1912 from necropsies on vagrants in Rangoon. In 1932 Stanton and Fletcher, of the Institute for Medical Research, Kuala Lumpur, Malaya, collected 83 cases of human infection from the literature—six of them in Europeans, and only nine of which were diagnosed before death. In this series there were only two survivors. Couture in 1935 reported 35 cases with a 95% mortality, and since then single instances or small series of cases have been recorded by a number of authors.

In the past the disease has been restricted to that part of Asia east and south-east of India, but in recent years isolated cases have been reported in Great Britain, the U.S.A., and South Africa among nationals who have returned from periods of residence in these endemic regions.

We have recently seen three patients with this disease in Malaya. We report them because they demonstrate the successful outcome that may be expected in cases suitably treated, and also because, owing to the large numbers of men and women of various nationalities who visit Malaya, isolated cases may be expected almost anywhere in the world.

### Case 1

A 50-year-old male Chinese vegetable seller was admitted to the General Hospital, Kuala Lumpur, on March 21, 1955, complaining of cough and fever of two weeks' duration. There was much purulent sputum, at times blood-stained, and he was wasted and looked toxic. Temperature 100.6° F. (38.1° C.), pulse 120, respirations 30. There were signs of consolidation in the right infraclavicular region, and a pleural rub in the left mid-axillary line associated with a few moist sounds. Liver and spleen were not enlarged, and no lymph nodes were palpable. Hb 7.7 g. per 100 ml.; W.B.C. 11,800 per c.mm.; E.S.R. 83 mm. in one hour (Westergren). Sputum examination repeatedly negative for acid-fast bacilli. Radiography showed ill-defined patchy opacities in the upper zones of both lungs, with a larger homogeneous opacity in the left mid-zone peripherally (Special Plate, Fig. 1). There was a large soft-tissue swelling in the root of the neck on the left side.

A provisional diagnosis of pulmonary tuberculosis was made, and streptomycin, 1 g. daily, and isoniazid, 100 mg. thrice daily, were administered. By the eleventh day the fever had subsided, but treatment was continued up to a total of 31 g. of streptomycin. Despite this an abscess developed in the right supraclavicular fossa from which dark, offensive material was aspirated. No organism was demonstrated on smear, but some haemolytic streptococci

were grown on culture. Shortly afterwards a cold abscess developed over the upper dorsal spine, and on June 15, 1955, some cheesy material containing pus cells and Gram-positive cocci was aspirated from it, but culture for tubercle bacilli proved negative. Radiography showed that the bone texture of the lower cervical and upper dorsal spine and the upper ribs was abnormally porotic (Special Plate, Fig. 2). A homogeneous opacity extended laterally over the apices of both lungs and appeared to be continuous with the soft-tissue swelling at the base of the neck; and on the left side the upper border of the second rib and the neck of the first rib were eroded. The possibility of infection with *Actinomyces* or some other unusual organism was suggested. The abscess was aspirated again and no fungi were found in the smears, but *Pf. whitmori* was grown on culture. It was found to be sensitive to chlortetracycline, oxytetracycline, chloramphenicol, and streptomycin.

From July 21 the patient was given chloramphenicol, 1 g. thrice daily, for 10 days; and then chlortetracycline, 500 mg. six-hourly, for seven days. There was a spectacular improvement in his condition, with steady return to normal weight and vigour. On July 26 the abscess was again aspirated and 1 g. of chloramphenicol injected into the cavity. The result was dramatic, and what had been a chronic abscess resolved completely within a few days. *X*-ray examination showed complete clearing of the pulmonary shadows, the texture of the bones affected had returned to normal, and new bone was visible under the anterior longitudinal ligament bridging the spaces between the bodies of C6 and C7. To date the patient remains fit and well.

### Case 2

A 42-year-old Chinese labourer was admitted to a small district hospital in Malaya on March 1, 1956, complaining of cough, purulent expectoration, fever, and progressive loss of weight. He was extremely emaciated and had a fever of 101° F. (38.3° C.). Some scattered soft crepitations were audible in both lungs. Hb 7.4 g. per 100 ml.; E.S.R. 65 mm. in one hour (Westergren). Sputum examinations were negative for tubercle bacilli, and blood films for malarial parasites. *X*-ray examination of the chest was interpreted as showing tuberculous infiltration in the left upper and middle zones with cavitation, and treatment with streptomycin, 1 g. daily, with P.A.S. and isoniazid was started. After 30 g. of streptomycin his condition was so improved that treatment was stopped; but because of a slight return of fever a second course was given, which lasted until June 14. A radiological opinion by one of us at this time was that there was a chronic abscess in the upper lobe of the left lung—probably not tuberculous (Special Plate, Fig. 3).

On June 20 a small abscess appeared in the suprasternal notch which gradually increased in size, and this was aspirated. No acid-fast bacilli were found on smear, but culture yielded a growth of *Pf. whitmori*. Sulphadiazine (total dose 36 g.) and chlortetracycline (total 37.5 g.) were then administered, and the abscess healed. His general condition continued to improve.

On September 8, 1956, he was admitted to the General Hospital, Kuala Lumpur, again complaining of cough. Repeated examination and culture of sputum proved negative. Radiography showed an increase in lung markings with soft, coarse mottled opacities scattered throughout both lung fields. Chloramphenicol, 250 mg. four times a day, was administered for nine days, and a second course of seven days' duration was given a month later. The cough ceased, but the radiographic appearances have remained unchanged for several months, although the patient has apparently fully recovered.

### Case 3

A 46-year-old Sikh watchman, who since 1948 had had insulin intermittently for diabetes, was admitted to the General Hospital, Kuala Lumpur, in November, 1955, with a history of fever and occasional rigors for three weeks and more recent development of a cough and thick, purulent sputum. He was very ill and emaciated and looked toxic. He had a hectic fever, and bronchial breathing was audible in the right mammary region. W.B.C. 9,000 per c.mm. (polymorphs 71%, lymphocytes 29%); Hb 12.6 g. per 100 ml. No acid-fast bacilli were found in the sputum in spite of repeated searches.

Radiography of the chest (Special Plate, Fig. 4) revealed a loculated hydropneumothorax on the right side. The right upper lobe was partially collapsed and contained a medium-sized abscess cavity surrounded by an irregular area of consolidation. Examination and culture of aspirated fluid revealed no organisms. Twelve days' treatment with 1.2 mega units of penicillin daily brought no improvement. Oxytetracycline, 2 g. daily, was then given. The response was dramatic, with an immediate fall of temperature and drying up of sputum, though a low night fever (99° F. —37.2° C.) continued. Weight increased, but further *x*-ray films of the chest showed little alteration.

A month after admission the pleural fluid had changed to thin, greenish pus and a broncho-pleural fistula developed. *Pf. whitmori*, sensitive to chloramphenicol and the tetracyclines, was isolated by culture. He was given 2 g. of chloramphenicol and 3 g. of chlortetracycline daily by mouth; and each day the empyema pockets were aspirated and 100 mg. of tetracycline solution and 500 mg. of chloramphenicol powder in suspension instilled. By the end of a week the lung had expanded well, and after another week the abscess in the right upper lobe was no longer visible on the radiographs. The patient was discharged two weeks later free of symptoms, having gained 30 lb. (13.6 kg.) in weight. A year later he was fit and well.

## Discussion

*Aetiology.*—The causative organism of melioidosis was first identified by Whitmore in 1913. But there is no general agreement on its classification, and it has been variously named *Pfeiferella whitmori, Pf. pseudomallei, Bacillus whitmori, Flavobacterium pseudomallei, Actinobacillus pseudomallei,* and *Loefflerella whitmori.* Morphologically it is very closely related to *Pf. mallei,* the organism responsible for glanders, from which it can be differentiated only on culture.

The mode or source of infection is unknown. At first Whitmore and Krishnaswami thought that the disease was the result of syringe inoculation, as many of their patients were morphine addicts, and they called it "morphine injector's septicaemia." Later Whitmore suggested that food contaminated with the excreta of infected rodents, probably rats, was the commonest source; and this theory has been accepted by several later observers in spite of the observations of Stanton and Fletcher (1932) and Alain *et al.* (1949) that it is rare to find rats infected with the disease in large surveys carried out to detect plague. Blanc and Baltazard (1941) showed that both the rat flea, *Xenopsylla cheopis,* and the mosquito, *Aëdes aegypti,* can harbour and transmit the organism, so that the possibility of an insect vector exists, especially as the disease has been known to occur in guinea-pigs, monkeys, rats, rabbits, dogs, and cats. Two fatal cases in horses have occurred in Malaya, and infected goats have been found in Malaya and Australia.

The apparent immunity of laboratory technicians working with *Pf. whitmori* cultures, and of attendants handling infected laboratory animals, suggests that man is not readily susceptible. Hennessy (cited Stanton and Fletcher, 1932) records a case in which the infection

occurred at the site of a dog-bite; but direct man-to-man infection has never been reported, though cases with severe pulmonary changes and discharging abscesses have been nursed in general wards.

*Pathology.*—At necropsy lesions are frequently demonstrated in lungs or bowel, and it seems likely that infection is by ingestion or by inhalation of the organism. In all of our cases there were manifest pulmonary lesions, and we believe that these represented the original location of the disease.

The organism stimulates an acute inflammatory reaction and small abscesses are rapidly formed. These tend to coalesce and to increase in size, and, if superficial, to break down and discharge. Spread occurs directly along deep tissue planes, and dissemination by the blood stream is common, leading to numerous pyaemic abscesses, especially in the lung, liver, spleen, and kidney, and usually to the early death of the patient. Enlargement of draining lymph nodes does not seem to be a feature of the disease, though abscesses in the neck —often the lower cervical region—are not uncommon. When bone is involved it undergoes necrosis. Sometimes only the skin may be affected, as described by de Moor *et al.* (1932) and Sudibyo (1938), and presents as a nodular skin eruption or indolent ulcers with raised nodular edges.

*Clinical Course.*—The disease may present in many different ways; occasionally in a fulminating form, as a septicaemia, cholera, or severe bronchopneumonia, with extreme prostration and death within a few days. More commonly it runs a slower, but, in the absence of treatment, equally relentless and fatal, course of a few weeks or months. Gastro-intestinal symptoms may suggest dysentery or typhoid; or pulmonary manifestations may be those of a lobar pneumonia or lung abscess, or may resemble miliary tuberculosis. A severe pyelitis or cystitis may accompany other lesions, or be the presenting form of the disease. A pustular form has been described which bears a superficial resemblance to smallpox.

At the other end of the scale is the rare, apparently benign, form with no constitutional disturbances, the patient presenting with superficial abscesses from which the organism is obtained. One of us has recently seen such a case in a Malay rice farmer who presented with a large abscess on his forearm from which *Pf. whitmori* was isolated. With treatment, which consisted in giving chloramphenicol by mouth and aspirating the abscess, his recovery was rapid.

Occasionally cases survive the acute stage of the disease and progress to a subacute or chronic stage which lasts anything from several months to several years; and some cases present as a subacute or chronic progressive illness from the start. It is of interest to note that of the cases so far reported in the white races almost all have been of this type. There is no constant pattern of this form of the disease other than a subacute pyaemia, with the development of chronic abscesses in almost any part of the body, which may lead to persistent discharging sinuses. Pulmonary involvement is common, either in the form of an irregular nodular infiltration which progresses to a spreading suppurative pneumonia, or as a chronic empyema. The disease may present as a liver abscess which is usually at first mistaken for amoebiasis. Bone involvement is not uncommon.

*Diagnosis.*—Final diagnosis depends on isolation of the causative organism. Its recovery has been reported from pus, blood, urine, cerebrospinal fluid (Martin, cited Stanton and Fletcher, 1932), and sputum. Usually a direct smear or *in vitro* culture is positive, though it may be necessary to examine a number of different specimens. Occasionally the diagnosis is made only after guinea-pig inoculation. In spite of the fact that all three of our cases had manifestations of pulmonary disease, in none was the organism isolated from the sputum.

Serological tests are not of much help in the diagnosis of the more acute forms of the disease, because the patient usually dies before the antibody titre is appreciably raised. Indeed, it is doubtful if agglutination tests are of any value even in more chronic forms, for titres ranging from 1:10 to 1:600 have been found in apparently healthy individuals in Malaya, and cases with active melioidosis may give titres of no more than 1:40.

Olds and Lewis (1954) claim that a filtered concentrated extract of a broth culture of *Pf. whitmori* (melioidin) causes typical positive skin reactions when injected into goats suffering from active disease. So far this method has not been tried in man. Gutner and Fisher (1948) reported a persistently positive Paul–Bunnell reaction in high dilution in their case, and they suggest that melioidosis may be another source of false positive heterophile antibody reactions.

*Radiology.*—In all our cases the possibility of an unusual disease was suggested, and this led to a search for one of the rarer organisms and the successful isolation of *Pf. whitmori.*

*Treatment.*—Grant and Barwell (1943) were the first to report the beneficial effect of sulphonamides. Of these, sulphathiazole and sulphadiazine are probably the most effective. The organisms are also sensitive to certain antibiotics, though different strains vary considerably in this respect. The most generally effective antibiotics seem to be chlortetracycline and chloramphenicol. In seriously ill patients it is advisable to use a combination of antibiotics and sulphonamides, but sensitivity tests must be carried out in each case.

*Conclusion.*—The possibility of melioidosis should be kept in mind in any unexplained suppurative pulmonary disease in a patient living in, or recently returned from, south-east Asia. The organism should be particularly looked for if there are multiple abscesses, discharging sinuses, or evidence of bone involvement.

## Summary

Melioidosis is an uncommon, but extremely serious, disease in man. Hitherto it has been almost entirely restricted to the inhabitants of south-east Asia, but in recent years cases have been reported in Great Britain, America, and south-east Africa among nationals who have returned from the Far East.

Three cases recently seen in Malaya are described because they illustrate the success of appropriate treatment in a condition which is almost invariably fatal if unrecognized.

The aetiology, pathology, clinical features, and treatment are briefly discussed.

We wish to thank the Director of Medical Services, Federation of Malaya, for permission to publish this paper, and to express our appreciation to Dr. John Whelan, senior

bacteriologist, Institute for Medical Research, Kuala Lumpur, for the personal attention he gave to all our requests for bacteriological examinations.

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# CHARCOT'S ARTHROPATHY FOLLOWING INTRA-ARTICULAR HYDROCORTISONE

BY

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[WITH SPECIAL PLATE]

In 1868 Charcot described a group of cases of arthritis associated with locomotor ataxy and hemiplegia, and stressed the absence of the cardinal signs of inflammation in the involved joints. He attributed the absence of pain to joint anaesthesia ("L'absence de douleur dans ces cas pourrait dépendre de l'anesthésie articulaire"). Eloesser (1917) reproduced the pathological features of this condition by repeated joint trauma in cats whose limbs had been rendered anaesthetic by severance of the posterior nerve roots. This work was thought to confirm the theory of pathogenesis which attributes these neuropathies to the effect of single or repeated injuries to a joint which has lost its sensibility to pain. Soto-Hall and Haldeman (1940) studied 40 patients with neuropathic joint disease. These authors showed that the essential features, in order of development, were the appearance of joint effusion, followed by ligamentous relaxation leading to instability and deformity with thinning of the articular cartilage. Marginal fractures, subchondral bony sclerosis, patchy atrophy, loose-body formation, and new bone production completed the picture of severe destructive arthritis.

The use of hydrocortisone acetate by intra-articular injection in the local treatment of arthritis has become widely accepted since its introduction in 1951 by Hollander and others. Most reports stress the subjective benefit derived by patients. Side-reactions are few, and are limited to temporary local exacerbation of disease, occasional appearance of sensitivity, the introduction of sepsis, and the development of thrombophlebitis in the injected leg. Hollander (1953) reported an incidence of only 2.3% of adverse reactions after 8,696 hydrocortisone injections. Kendall (1958) had an even lower incidence (1.1%) of untoward effects in a series of 6,700 injections. There has been no suggestion that repeated intra-articular injections of hydrocortisone might seriously aggravate arthritis, yet such aggravation might be expected as a result of the relief of pain experienced from such treatment. Interference with the normal protective processes might well encourage undue weight-bearing and mobility, thereby accelerating the progress of joint destruction. This has, in fact, been our experience in 10 of 18 patients with rheumatoid arthritis given prolonged treatment during a controlled trial of intra-articular steroid therapy (Chandler and Wright, 1958).

The following report describes the rapid deterioration of an osteoarthritic hip following repeated hydrocortisone injections.

## Case Report

A doctor's wife aged 66 was first seen in the Rheumatism Clinic of the General Infirmary at Leeds in May, 1956. She had had pain in the right hip with difficulty in walking since 1937. Apart from a course of physiotherapy given with temporary benefit in 1951, she had received no treatment. Radiography of the right hip at this time showed slight osteoarthritic change (Special Plate, Fig. 1).

Examination disclosed a thin, intelligent woman in obvious pain. Chest, heart, and abdomen were normal, and there was no neurological defect. The only abnormality was painful restriction of movement at the right hip-joint. There was no shortening of the limb. A radiograph of the right hip disclosed some progression of disease as compared with the earlier film. The differential agglutination test was negative and the erythrocyte sedimentation rate (E.S.R.) normal.

Treatment was begun with phenylbutazone, 200 mg. twice daily, and 50 mg. (2 ml.) of hydrocortisone acetate injected into the right hip-joint at approximately monthly intervals. After each injection she experienced great relief from pain, which lasted some three weeks on each occasion. Fig. 2 on the Special Plate shows the radiographic appearance six months after treatment was started. Injections were continued for a further 12 months, when 900 mg. (36 ml.) of hydrocortisone had been given. Re-examination then showed an extremely mobile, painless joint. There was 2 in. (5 cm.) of true shortening of the right leg. The rest of the clinical examination was negative. A radiograph of the right hip showed gross destruction of the femoral head and the roof of the acetabulum (Special Plate, Fig. 3). Blood Wassermann reaction was negative and E.S.R. normal.

Biopsy of the right hip (Mr. A. B. Pain) showed no unusual features in the portions of tendon and joint capsule examined (Dr. D. Harriman) beyond some non-specific connective-tissue proliferation and occasional small foci of foreign-body reaction. Muscular atrophy was advanced. Biopsy of bone examined by Professor C. E. Lumsden showed features of resorption (Special Plate, Fig. 4) and new bone formation (Special Plate, Fig. 5). One section of biopsy was sent to Professor D. H. Collins, who reported: "There are really no diagnostic features in this biopsy. Most of the bone in the section is of compact or cortical pattern and appears normal, but at its junction with the periosteal tissues there are certain progressive changes of resorption and regeneration such as one may encounter in any slow remodelling process. Rather large, thin-walled vascular spaces and some islets of new metaplastic bone are seen in part of the outlying connective tissues. There is no evidence of tuberculosis or other infection. The changes that we see may be encountered around an osteoarthritic joint or, indeed, a Charcot's joint, but there is nothing to

H. G. RICHMOND: SARCOMA INDUCTION BY IRON-DEXTRAN COMPLEX

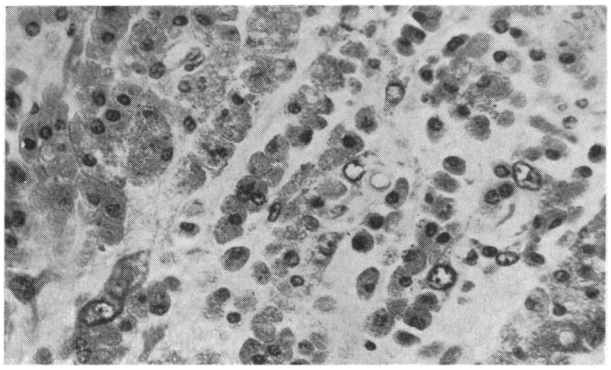

FIG. 1.—Biopsy of site of injection at 16 months. Iron-laden histiocytes mingled with aberrant cells. (H. and E. ×300.)

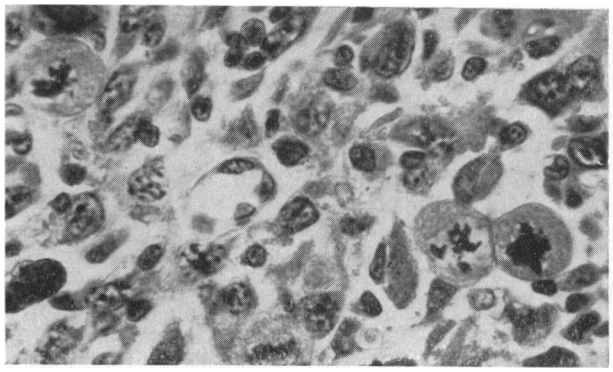

FIG. 2.—Biopsy from same rat as Fig. 1 five weeks later. Pleomorphic tumour showing numerous mitotic figures. (H. and E. ×450.)

B. S. KHAIRA, W. B. YOUNG, AND P. de V. HART: MELIOIDOSIS

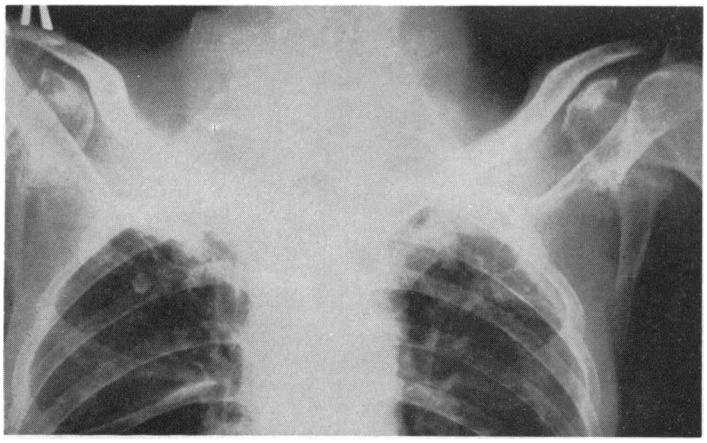

FIG. 1

FIG. 1.—Case 1. Ill-defined patchy opacities in upper zones of both lungs, with larger homogeneous opacity in left mid-zone peripherally.

FIG. 2.—Case 1. Porosis of lower cervical and upper dorsal spine and upper ribs.

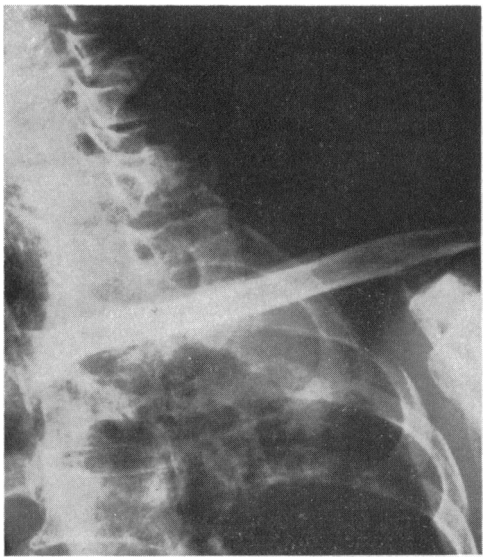

FIG. 2

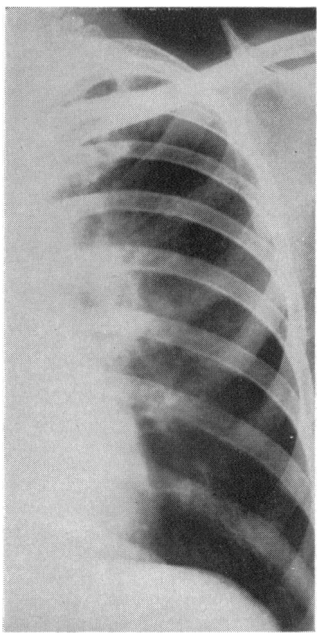

FIG. 3.—Case 2. Infiltration in left upper and middle zones of left lung.

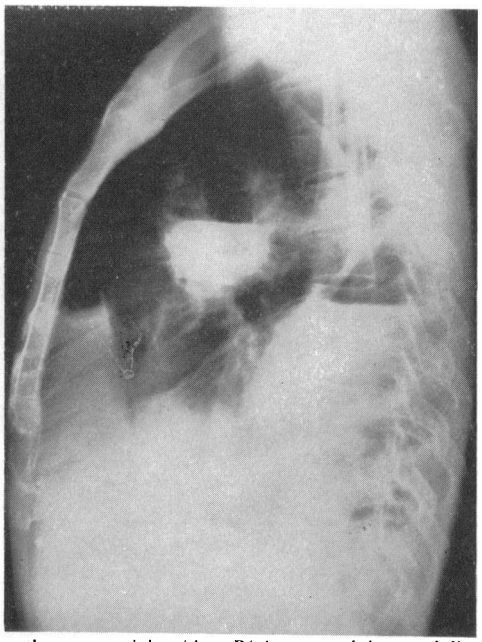

FIG. 4.—Case 3. Loculated hydropneumothorax on right side. Right upper lobe partially collapsed and containing medium-sized abscess cavity surrounded by irregular area of consolidation.